FILE 'AGRICOLA, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHDS, CABA, CANCERLIT, CAPLUS, CEABA, CIN, CONFSCI, DGENE, EMBASE, ESBIOBASE, FSTA, GENBANK, JICST-EPLUS, LIFESCI, MEDLINE, NTIS, PROMT, SCISEARCH, TOXLINE'
ENTERED AT 17:58:32 ON 11 AUG 2000

L1	27456	S N-ACETYLCYSTEINE OR 616-91-1
L2	199762	S ASCORBIC ACID OR 50-81-7
L3	3742	S .ALPHA.-LIPOIC ACID OR 1200-22-2
L4	17553	S QUERCITIN OR 117-39-5
L5	145729	S GLUTAMINE OR 56-85-9
L6	37168	S N-ACETYLGLUCOSAMINE OR 7512-17-6
L7	1	S L1 AND L2 AND L3 AND L4 AND L5 AND L6 > applicant
L8	1	S L1 AND L2 AND L3 AND L4 AND L5
L9	5	S L1 AND L2 AND L3 AND L4
L10	0	S L9 AND (GLUTATHIONE (S) (STIMULAT? OR ENHANC? OR AUGMENT?))
L11	5	DUP REM L9 (0 DUPLICATES REMOVED)
L12	27	S L1 AND L2 AND L3
L13	17	S L12 AND (GLUTATHIONE)
L14	17	DUP REM L13 (0 DUPLICATES REMOVED)
L15	2	S L12 AND (GLUTATHIONE (S) (PRODUC? OR LEVEL?))
L16	2	DUP REM L15 (0 DUPLICATES REMOVED)
L17	0	S L12 AND GLUTATHIONE AND SYLMARIN
L18	2	S L12 AND (GLUTATHIONE AND (SYLIMARIN OR SILIBIN OR SILYBIN OR
L19	2	DUP REM L18 (0 DUPLICATES REMOVED)
L20	1246	S L1 AND L2
L21	600	S L20 AND GLUTATHIONE
L22	106	S L20 AND (GLUTATHIONE (S) (STIMULAT? OR ENHANC? OR AUGMENT?))
L23	56	S L20 AND (GLUTATHIONE (S) (STIMULAT? OR ENHANC? OR AUGMENT?)
L24	22	DUP REM L23 (34 DUPLICATES REMOVED)
L25	23	S L23 AND (FATIGUE OR T-CELL OR CHOLESTEROL OR STRESS)
L26	10	DUP REM L25 (13 DUPLICATES REMOVED)

try @ 50-81-7 (S) (uptake or transport) (C) N-AC

No 102(6)

L11 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS
TI Method of treatment of glutathione deficient mammals
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
IN Keller, M. D. Robert H.; Kirchenbaum, David W.
AB Glutathione is a tripeptide of extreme importance as a catalyst, reductant, and reactant. The disclosure is of a unique combination of nutritional supplements including **N-acetylcysteine**, vitamin C, L-glucosamine, N-acetyl-D-glucosamine, **quercitin**, sylimarin, **.alpha.-lipoic acid**, and high-protein, low-fat whey that are combined to support various bodily systems involved in glutathione synthesis, reutilization and storage, all intended to elevate glutathione concn. in the mammalian cell.

L11 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2000 ACS
TI Composition and method for treating rosacea and sensitive skin with free radical scavengers
SO U.S., 11 pp.
CODEN: USXXAM
IN Ptchelintsev, Dmitri
AB A method for treating skin conditions, such as rosacea and sensitive skin, that manifest as a tendency towards flushing and blushing is provided. Also provided herein, are compns. for the treatment of rosacea and sensitive skin that are comprised of at least one antioxidant selected from the following groups of antioxidants: (a) phenolic compds. that contain at least one hydroxyl group connected directly to a benzene ring and to another unsatd. chem. grouping, (b) sulfur-contg. compds. that contain at least one sulfhydryl groups or sulfur-contg. compds. that contain at least one disulfide group, or (c) polyene compds. that have conjugated systems of double bonds. A compn. contained mixed tocopherols 1.0, vitamin E succinate 1000, PEG 0.5, gamma oryzanol 0.2, lipoic acid 0.1, hesperetin 0.1, naringenin 0.1, Silybin (silymarin) 0.1, chlorogenic acid 0.01, and vehicle 97.89%. Efficacy of the compn. in treatment of women having rosacea for 8 wk is reported.

L11 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2000 ACS
TI Compounds and their combinations for the treatment of influenza infection
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
IN Jones, Dean P.; Furukawa, Satoru
AB Administration of one or more of glutathione, its disulfide dimer, ascorbate 2-phosphate, or N-acetyl-L-cysteine, with or without antioxidants, is suitable for the treatment of influenza virus infection, as well as prophylactic prevention of influenza virus infection. Synthetic procedures are given for the compds., as well as pharmacol. data of the effect of the compds. on influenza virus. Also formulation examples are given, e.g., a nasal spray contg. glutathione (1.0g).

L11 ANSWER 4 OF 5 BIOBUSINESS COPYRIGHT 2000 BIOSIS
TI Antioxidants: One size doesn't fit all.
SO Natural Foods Merchandiser, (1998) Vol.19, No.3, March, p.134,136,144.
ISSN: 0164-338X.
AU Challem J

L11 ANSWER 5 OF 5 PROMT COPYRIGHT 2000 Gale Group

TI BioDynamax Supplement - Ultra Antioxidants Tablets MANUFACTURER: BioDynamax CATEGORY: Vitamins & Tonics

SO Product Alert, (Dec 1997) pp. N/A.
ISSN: 0740-3801.

AB BioDynamax Ultra Antioxidants have been reformulated "to provide the most comprehensive antioxidant protection in one convenient formula." This two-tablet per day Supplement contains a combination of 21 antioxidants: beta-carotene, vitamin C, vitamin E, **N-acetylcysteine,** green tea, garlic, milk thistle, hawthorn, turmeric, quercetin, red wine extract, rosemary extract, boldo, zinc, **alpha-lipoic acid**, grape seed extract, ginkgo biloba extract, bioperine, manganese, copper and selenium. Bioperine is a trademark of the Sabinsa Corp. Tablets come in 45 ct. and 90 ct. bottles tagged, "Extra strength," with suggested retail prices of $9.19 and $20.39, respectively. Boulder, CO-based BioDynamax is the manufacturer. For sample retrieval information, please call: Marketing Intelligence Service, Ltd., (716) 374-6326.

shows combination of N-Ac-cys + α-lipoic acid

L16 ANSWER 1 OF 2 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system.
SO Blood, (1 Jan 1999) 93/1 (268-277).
Refs: 51
ISSN: 0006-4971 CODEN: BLOOAW
AU Dai J.; Weinberg R.S.; Waxman S.; Jing Y.
AB Arsenic trioxide (As2O3) induces clinical remission in acute promyelocytic leukemia (APL) with minimal toxicity and apoptosis in APL- derived NB4 cells at low (1 to 2 .mu.mol/L) concentration. We examined the basis for NB4 cell sensitivity to As2O3 to identify experimental conditions that would render other malignant cells responsive to low concentrations of As2O3. The intracellular **glutathione** (GSH) content had a decisive effect on As2O3-induced apoptosis. Highly sensitive NB4 cells had the lowest GSH and the sensitivity of other cell lines was inversely proportional to their GSH content. The t(14;18) B-cell lymphoma cell line had low GSH **levels** and sensitivity to As2O3 at **levels** slightly higher than in APL cells. Experimental upmodulation of GSH content decreased the sensitivity to As2O3. **Ascorbic acid** and buthionine sulfoxide (BSO) decreased GSH to a greater extent, and rendered malignant cells more sensitive to As2O3. As2O3-induced apoptosis was not enhanced by **ascorbic acid** in normal cells, suggesting that the combination of **ascorbic acid** and As2O3 may be selectively toxic to some malignant cells. **Ascorbic acid** enhanced the antilymphoma effect of As2O3 in vivo without additional toxicity. Thus, As2O3 alone or administered with **ascorbic acid** may provide a novel therapy for lymphoma.

L16 ANSWER 2 OF 2 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Effects of antioxidants on nerve and vascular dysfunction in experimental diabetes.
SO Diabetes Research and Clinical Practice, (1999) 45/2-3 (137-146).
Refs: 67
ISSN: 0168-8227 CODEN: DRCPE
AU Cameron N.E.; Cotter M.A.
AB Reactive oxygen species (ROS) are elevated by metabolic changes in diabetes, including autoxidation and increased advanced glycation. Endogenous protection by the **glutathione** redox cycle is also compromised by the competing NADPH requirement of elevated polyol pathway flux. Antioxidant treatment strategies prevent or reverse nerve conduction velocity (NCV) deficits in diabetic rats. These include lipophilic scavengers such as butylated hydroxytoluene, probucol and vitamin E, more hydrophilic agents like .**alpha**.-**lipoic acid** and acetyl cysteine, and transition metal chelators that inhibit autoxidation. In the long-term, elevated ROS cause cumulative damage to neurons and Schwann cells, however, they also have a deleterious effect on nerve blood flow in the short term. This causes endoneurial hypoxia, which is responsible for early NCV deficits. Antioxidant treatment corrects the blood flow deficit and promotes normal endoneurial oxygenation. ROS cause antioxidant-preventable vascular endothelium abnormalities, neutralizing nitric oxide mediated vasodilation and increasing reactivity to

vasoconstrictors. Unsaturated fatty acids are a major target for ROS and essential fatty acid metabolism is impaired by diabetes. .gamma.-Linolenic acid stimulates vasodilator prostanoid **production**, and there are marked synergistic interactions between .gamma.-linolenic acid and antioxidants. This has encouraged the development of novel drugs such as ascorbyl-.gamma.-linolenic acid and .gamma.-linolenic acid-lipoic acid with enhanced therapeutic potential.

L19 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS
TI Method of treatment of **glutathione** deficient mammals
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
IN Keller, M. D. Robert H.; Kirchenbaum, David W.
AB **Glutathione** is a tripeptide of extreme importance as a catalyst, reductant, and reactant. The disclosure is of a unique combination of nutritional supplements including **N-acetylcysteine**, vitamin C, L-glucosamine, N-acetyl-D-glucosamine, quercitin, **sylimarin**, .**alpha**.-**lipoic acid**, and high-protein, low-fat whey that are combined to support various bodily systems involved in **glutathione** synthesis, reutilization and storage, all intended to elevate **glutathione** concn. in the mammalian cell.

L19 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS
TI Composition and method for treating rosacea and sensitive skin with free radical scavengers
SO U.S., 11 pp.
CODEN: USXXAM
IN Ptchelintsev, Dmitri
AB A method for treating skin conditions, such as rosacea and sensitive skin, that manifest as a tendency towards flushing and blushing is provided. Also provided herein, are compns. for the treatment of rosacea and sensitive skin that are comprised of at least one antioxidant selected from the following groups of antioxidants: (a) phenolic compds. that contain at least one hydroxyl group connected directly to a benzene ring and to another unsatd. chem. grouping, (b) sulfur-contg. compds. that contain at least one sulfhydryl groups or sulfur-contg. compds. that contain at least one disulfide group, or (c) polyene compds. that have conjugated systems of double bonds. A compn. contained mixed tocopherols 1.0, vitamin E succinate 1000, PEG 0.5, gamma oryzanol 0.2, lipoic acid 0.1, hesperetin 0.1, naringenin 0.1, **Silybin** (silymarin) 0.1, chlorogenic acid 0.01, and vehicle 97.89%. Efficacy of the compn. in treatment of women having rosacea for 8 wk is reported.

L19 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:708599 CAPLUS
DOCUMENT NUMBER: 131:317792
TITLE: Method of treatment of **glutathione** deficient mammals
INVENTOR(S): Keller, M. D. Robert H.; Kirchenbaum, David W.
PATENT ASSIGNEE(S): Vit-Immune, L.C., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
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FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9955326	A1	19991104	WO 1999-US9485	19990429
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1998-83661	19980430

REFERENCE COUNT: 1
REFERENCE(S): (1) Sharma, S; Cancer Research 1994, V54(22), P5848

L26 ANSWER 1 OF 10 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
TI Involvement of oxidative **stress** in tumor cytotoxic activity of hepatocyte growth factor/scatter factor.
SO Journal of Biological Chemistry, (May 7, 1999) Vol. 274, No. 19, pp. 13541-13546.
ISSN: 0021-9258.
AU Arakaki, Naokatu; Kajihara, Takehiro; Arakaki, Rieko; Ohnishi, Tomokazu; Kazi, Jamil Ahsan; Nakashima, Hideki; Daikuhara, Yasushi (1)
AB In this study, we show that **N-acetylcysteine** (NAC), a precursor of **glutathione** and an intracellular free radical scavenger, almost completely prevented hepatocyte growth factor (HGF)-suppressed growth of Sarcoma 180 and Meth A cells, and HGF-induced apoptosis, assessed by DNA fragmentation, and increase in caspase-3 activity, in Sarcoma 180 cells. The reduced form of **glutathione** also prevented HGF-suppressed growth of the cells as effective as NAC. **Ascorbic acid** partially prevented the effect of HGF, but other antioxidants such as superoxide dismutase, catalase, and vitamin E, and the free radical spin traps N-t-butyl-alpha-phenylnitrone and 3,3,5,5-tetramethyl-1-pyrroline-1-oxide did not have protective effects. HGF caused morphological changes of the cells, many cells showing condensation and rounding, and **enhanced** the generation of intracellular reactive oxygen species (ROS) as judged by flow cytometric analysis using 2',7'-dichlorofluorescein diacetate. NAC completely prevented both HGF-induced morphological changes and the **enhancement** of ROS generation in the cells. However, NAC did not prevent the HGF-induced scattering of Madin-Darby canine kidney cells. To our knowledge, this is the first report that HGF **stimulates** the **production** of ROS, and our results suggest the involvement of oxidative **stress** in the mechanism by which HGF induces growth suppression of tumor cells.

L26 ANSWER 2 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Chloroacetonitrile-induced toxicity and oxidative **stress** in rat gastric epithelial cells.
SO Pharmacological Research, (1999) 40/4 (377-383).
Refs: 36
ISSN: 1043-6618 CODEN: PHMREP
AU Mohamadin A.M.; Abdel-Naim A.B.
AB Chloroacetonitrile (CAN), is a disinfectant by-**product** of chlorination of drinking water. Epidemiological studies indicate that exposure to CAN via drinking water might present a potential hazard to human health. The objective of the present work was to investigate the cytotoxic effects as well as the oxidative **stress** induced by CAN in cultured rat gastric epithelial cells (GECs). GECs were exposed in vitro to different concentrations of CAN (5-40 .mu.M) for 60 min. Also, GECs were incubated with CAN (10 .mu.M) for different time intervals extending to 180 min. Cytotoxicity was determined by assessing cell viability and lactate dehydrogenase (LDH) release, **glutathione** (GSH) **level** and lipid peroxidation as indicated by malondialdehyde (MDA) **production**. Exposure of GECs CAN (10 .mu.M) for 60 min caused a 50% decrease in cell viability and induced an eightfold increase of LDH leakage. In the same experiment, CAN caused a decrease in cellular GSH content to approximately 50% and significantly **enhanced** MDA accumulation (approx, sevenfold). These toxic responses to CAN were dependent on both concentration and duration of exposure to CAN. There was a good correlation between LDH release and GSH depletion ($r = 0.96$, $P < 0.05$). Treatment of GECs with 5 mM N-acetyl-L-cysteine (NAC) prior to exposure to CAN afforded some degree

of

protection as indicated by a significant decrease in the LDH leakage (32% of total leakage) and lipid peroxidation (54%) as compared to CAN alone-treated cells. Also, pretreatment of GECs with vitamin C (1 mM or vitamin E (10 .mu.M) significantly inhibited LDH leakage (20 and 36% of total leakage, respectively). Preincubation with 1 mM desferroxiamine (DFO), a ferric iron chelator, or 10 .mu.M phenanthroline (PHE), a ferrous iron chelator, diminished CAN-induced LDH leakage by 16 and 21% of total leakage, respectively and MDA **production** by 40 and 44%, respectively. In conclusion, our results suggest that CAN has a potential cytotoxic effect in rat GECs; and thiol group-donors, antioxidants and iron chelators can play a critical role against CAN-induced cellular damage.

L26 ANSWER 3 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Schisandrin B protects against myocardial ischemia-reperfusion injury by enhancing myocardial glutathione autioxidant status.
SO Molecular and Cellular Biochemistry, (1999) 196/1-2 (151-156).
Refs: 24
ISSN: 0300-8177 CODEN: MCBIB8
AU Yim T.K.; Ko K.M.
AB The effects of Schisandrin B (Sch B) and dimethyl-4,4'-dimethoxy-5,6,5',6'dimethylene-dioxy-biphenyl-2,2'-bicarboxylate (DDB) treatment on myocardial ischemia-reperfusion (IR) injury in isolated perfused rat hearts were examined under both in vitro and ex vivo conditions. In vitro administration of liposome-entrapped Sch B or DDB during reperfusion did not protect against myocardial IR injury, whereas **ascorbic acid** or Trolox supplemented perfusate **produced** protective effect, as evidenced by the significant decrease in the extent of lactate dehydrogenase leakage as well as an improvement in contractile force recovery. Myocardial protection afforded by N-acetyl-L-cysteine supplemented perfusate was not accompanied by the **enhancement** in contractile force recovery. In ex vivo experiment, pretreatment of Sch B (0.6/1.2 mmol/kg/day x 3) protected against IR-induced myocardial damage in a dose-dependent manner. The myocardial protection was associated with an **enhancement** in myocardial **glutathione** antioxidant status, as indicated by significant reductions in both the extent of IR-induced reduced **glutathione** depletion and inhibition of Se-**glutathione** peroxidase and **glutathione** reductase activities. In contrast, the inability of DDB pretreatment to **enhance** myocardial **glutathione** antioxidant status resulted in a failure in preventing IR injury. The ensemble of results suggests that the myocardial protection afforded by Sch B pretreatment, which was unlikely due to free radical scavenging action, may be mainly mediated by the **enhancement** of myocardial **glutathione** antioxidant status, particularly under oxidative **stress** conditions.

L26 ANSWER 4 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Improvement by several antioxidants of macrophage function in vitro.
SO Life Sciences, (31 Jul 1998) 63/10 (871-881).
Refs: 46
ISSN: 0024-3205 CODEN: LIFSAK
AU Del Rio M.; Ruedas G.; Medina S.; Victor V.M.; De la Fuente M.
AB The toxic effects of oxygen radicals **produced** by immune cells can be controlled to certain degree by endogenous antioxidants, because of their scavenger action. This control is specially important in a type of immune cell, i.e.: the phagocyte, which needs oxygen free radicals and uses antioxidants in order to support its functions. Previous studies have shown an **stimulation** of the immune system with an antioxidant enriched diet. In the present work, we have studied the effects in vitro of several antioxidants: .alpha.-tocopherol or vitamin E (VE), **ascorbic acid** (AA), **glutathione** (GSH),

N- acetylcysteine (NAC) and thioproline or thiazolidine-4-carboxylic acid (TCA), at different concentrations, on the various steps of the phagocytic process of murine peritoneal macrophages, i.e.: adherence to substrate, migration (random migration and directed migration or chemotaxis), ingestion and superoxide anion **production**. The results show an antioxidant-induced **stimulation** of the phagocytic process of macrophages. Thus, the adherence to substrate was raised, after short incubation times, by .alpha.-tocopherol and **ascorbic acid**. Random migration, chemotaxis, ingestion and superoxide anion **production** were increased by all the antioxidants used.

L26 ANSWER 5 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Neurodegenerative disorders in humans: The role of glutathione in oxidative **stress**-mediated neuronal death.
SO Brain Research Reviews, (1997) 25/3 (335-358).
Refs: 315
ISSN: 0165-0173 CODEN: BRERD2
AU Bains J.S.; Shaw C.A.
AB Oxidative **stress** has been implicated in both normal aging and in various neurodegenerative disorders and may be a common mechanism underlying various forms of cell death including necrosis, apoptosis, and excitotoxicity. In this review, we develop the hypothesis that oxidative **stress**-mediated neuronal loss may be initiated by a decline in the antioxidant molecule **glutathione** (GSH). GSH plays multiple roles in the nervous system including free radical scavenger, redox modulator of ionotropic receptor activity, and possible neurotransmitter. GSH depletion can **enhance** oxidative **stress** and may also increase the **levels** of excitotoxic molecules; both types of action can initiate cell death in distinct neuronal populations. Evidence for a role of oxidative **stress** and diminished GSH status is presented for Lou Gehrig's disease (ALS), Parkinson's disease, and Alzheimer's disease. Potential links to the Guamnian variant of these diseases (ALS-PD complex) are discussed. In context to the above, we provide a GSH-depletion model of neurodegenerative disorders, suggest experimental verifications of this model, and propose potential therapeutic approaches for preventing or halting these diseases.

L26 ANSWER 6 OF 10 JICST-EPlus COPYRIGHT 2000 JST
TI Cytotoxicity of Dopamine, L-DOPA and 6-Hydroxydopamine on Cultured Human Leukemia Cells. I.
SO Tohoku Yakka Daigaku Kenkyu Nenpo (Annual Report of Tohoku College of Pharmacy), (1997) no. 44, pp. 231-239. Journal Code: G0653A (Fig. 6, Ref. 23)
CODEN: TYKNAQ; ISSN: 0495-7342
AU SASAKI TAKAKO; HAREYAMA SHIZUE; ISHIKAWA MASAAKI; TAKAYANAGI MOTOAKI; TAKAYANAGI YOSHIO; SASAKI KEN'ICHI
AB **Enhanced** oxidative **stress** has been suggested to be involved in the degeneration of nigrostriatal dopaminergic neurons in Parkinson's disease. One of the proposed mechanisms of dopamine-, L-.BETA.-3,4-dihydroxyphenylalanine(L-DOPA)- and 6-hydroxydopamine-induced cytotoxicity is generation of activated oxygen species, all of which are either free radical or potentially free radical species. In human leukemia cells (K562, Jurkat and HL60 cell lines), cytotoxicity by dopamine, L-DOPA and 6-hydroxydopamine was measured by using MTT method and multiparametric flowcytometric determination of cellular propidium iodide. Dopamine, L-DOPA and 6-hydroxydopamine **produced** a time- and dose-dependent

increase in cell death in human leukemia cells. Depletion of **glutathione** by inhibition of its synthesis by buthionine sulfoximine, an irreversible inhibitor of .GAMMA.-glutamylcysteine synthetase, led an increased sensitivity to dopamine-induced cytotoxicity in K562 cells. When, an intracellular cysteine delivery system was used to promote **glutathione** synthesis, it found to protect against cytotoxicity. The non-enzymatic antioxidants such as **glutathione** and **N-acetylcysteine** protected, but not **ascorbic acid**, against dopamine-induced cytotoxicity in Jurkat cells. These results indicate that **glutathione** plays an important role in dopamin-, L-DOPA- and 6-hydroxydopamine-induced cytotoxicity in human leukemia cells. (author abst.)

L26 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
TI Prevention of dopamine-induced cell death by thiol antioxidants: Possible implications for treatment of Parkinson's disease.
SO Experimental Neurology, (1996) Vol. 141, No. 1, pp. 32-39.
ISSN: 0014-4886.
AU Offen, Daniel (1); Ziv, Ilan (1); Sternin, Hagit; Melamed, Eldad (1); Hochman, Ayala
AB We have recently shown that dopamine (DA) can trigger apoptosis, an active program of cellular self-destruction, in various neuronal cultures and proposed that inappropriate activation of apoptosis by DA and or its oxidation **products** may initiate nigral cell loss in Parkinson's disease (PD). Since DA toxicity may be mediated via generation of oxygen-free radical species, we examined whether DA-induced cell death in PC12 cells may be inhibited by antioxidants. We have found that the thiol containing compounds, reduced **glutathione** (GSH), N-acetyl-cysteine (NAC), and dithiothreitol (DTT) were markedly protective, while vitamins C and E had lesser or no effect. The thiol antioxidants and vitamin C but not vitamin E, prevented dopamine autooxidation and **production** of dopamine-melanin. Their protective effect has also manifested by inhibiting DA-induced apoptosis; DNA fragmentation was prevented as was shown histochemically by the in situ end-labeled DNA technique (TUNEL). Intracellular GSH and other thiols constitute an important natural defense against oxidative **stress**. We have found that depletion of cellular GSH by the addition of phoron, a substrate of **glutathione** transferase, and buthionine sulfoximine (BSO), an inhibitor of gamma-glutamyl transpeptidase, significantly **enhanced** DA toxicity. Cotreatment with NAC rescued the cells from the toxic effect of BSO + DA, and phoron + DA, while addition of GSH provided only partial protection from BSO + DA toxicity. Our data indicate that the thiol family of antioxidants, but not vitamins C and E, are highly effective in rescuing cells from DA-induced apoptosis.
Further study of the mechanisms underlying the unique protective capacity of thiol antioxidants may lead to the development of new neuroprotective therapeutic strategies for PD.

L26 ANSWER 8 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Inhibitors of oxidative **stress** mimic the ability of follicle-stimulating hormone to suppress apoptosis in cultured rat ovarian follicles.
SO Endocrinology, (1995) 136/1 (242-252).
ISSN: 0013-7227 CODEN: ENDOAO
AU Tilly J.L.; Tilly K.I.
AB We have reported that members of the bcl-2 gene family are expressed and gonadotropin regulated in ovarian granulosa cells during follicular maturation and atresia. Because Bcl-2, a protein that prevents apoptosis in several cell types, is reported to function as an antioxidant or free radical scavenger, the present studies were designed to investigate if

oxidative **stress** plays a role in granulosa cell apoptosis during follicular atresia in the immature rat ovary. In the first series of experiments, the role of oxidative **stress** in the induction of granulosa cell apoptosis was directly tested using a defined in vitro follicle culture system. Healthy antral follicles obtained from equine CG (eCG)-primed immature (27 day old) rats were incubated in serum-free medium for 24 h in the absence or presence of FSH (100 ng/ml; a control for inhibiting apoptosis), superoxide dismutase (SOD; 10-1000 U/ml, **ascorbic acid** (0.01-1 mM; a free radical scavenger), N-acetyl-L-cysteine (25-100 mM; a free radical scavenger and **stimulator** of endogenous **glutathione** peroxidase activity), or catalase (10-1000 U/ml. Granulosa cells within follicles incubated in medium alone exhibited extensive apoptosis after 24 h of incubation, and this onset of apoptosis was blocked by treatment with FSH (29 .+-. 4% of controls; P < 0.001, n = 3). Moreover, apoptosis in follicles was also inhibited by treatment with SOD (44 .+-. 4% of controls at 1000 U/ml; P < 0.01, n = 3), **ascorbic acid** (55 .+-. 9% of controls at 1 mM; P < 0.05, n = 3), N-acetyl-L-cysteine (24 .+-. 7% of controls at 100 mM; P < 0.001,n = 3), or catalase (35 .+-. 6% of controls at 1000 U/ml; P < 0.001, n = 3). In the second series of experiments, complementary DNAs corresponding to secreted (SEC-SOD), copper/zinc-containing (Cu/Zn-SOD), and manganese-containing (Mn-SOD) forms of rat SOD, rat seleno-cysteine **glutathione** peroxidase (GSHPx), and rat catalase were isolated and used to synthesize antisense RNA probes for Northern and slot blot analysis of changes in SOD, GSHPx, and catalase gone expression during follicular maturation. In vivo priming of 25-day-old female rats for 2 days with 10 IU eCG, which promoted antral follicular growth and survival, increased **levels** of messenger RNA encoding SEC-SOD (216 .+-. 9% of saline-treated controls, P < 0.05, n = 3) and Mn-SOD (222 .+-. 14% of saline-treated controls, P < 0.05, n = 3) vs. saline-treated controls. However, gonadotropin priming did not alter expression of Cu/Zn-SOD, GSHPx, or catalase messenger RNA in the ovary. Nevertheless, the induction of SEC-SOD and Mn-SOD expression by eCG provided further evidence that gonadotropins may promote granulosa cell survival in developing antral follicles via activation of an oxidative **stress** response. Collectively, these data suggest that the gonadotropin-mediated inhibition of follicular atresia involves **enhanced** expression of oxidative **stress** response genes whose **products** may then function to protect granulosa cells from the damaging effects of reactive oxygen species.

L26 ANSWER 9 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
TI Antioxidant status and lipid peroxidation in patients infected with HIV.
SO Chemico-Biological Interactions, (1994) 91/2-3 (165-180).
ISSN: 0009-2797 CODEN: CBINA8
AU Favier A.; Sappey C.; Leclerc P.; Faure P.; Micoud M.
AB Deficiency in antioxidant micronutrients have been observed in patients with AIDS. These observations concerning only some isolated nutrients demonstrate a defect in zinc, selenium, and **glutathione**. An increase in free radical **production** and lipid peroxidation has been also found in these patients, and takes a great importance with recent papers presenting an immunodeficiency and more important an increase in HIV-1 replication secondary to free radicals overproduction. We have assessed different studies, trying to obtain a global view of the antioxidant status of these patients. In adults we observe a progressive decrease for zinc, selenium, and vitamin E with the severity of disease, except that selenium remains normal at stage II. However, the main dramatic decrease concerns carotenoids whose **level** at stage II is only half the normal value. To understand if these decreases in antioxidant and increases in oxidative **stress** occur secondary to the aggravation of the disease or, conversely, are responsible for it, we

undertook a longitudinal survey of asymptotic patients. The preliminary results of this evaluation are presented. Paradoxically, lipid peroxidation is higher at stage II than at stage III. This may be consecutive to a more intense overproduction of oxygen free radicals by more viable polymorphonuclear (PMN) at the asymptomatic stage. The free radicals **production** and lipid peroxidation seem secondary to a direct induction by the virus of PMN **stimulation** and cytokines secretion. N-Acetyl cystein or ascorbate have been demonstrated in cell culture to be capable of blocking the expression of HIV-1 after oxidative **stress** and N-acetyl cysteine inhibits in vitro TNF-induced apoptosis of infected cells. In regard to all these experimental data, few serious and large trials of antioxidants have been conducted in HIV-infected patients, although some preliminary studies using zinc or selenium have been performed. In our opinion it is now time to evaluate in humans the beneficial effect of antioxidants. The more promising candidates for presenting synergistic effects when associated with N-acetyl cysteine seem to be .beta.-carotene, selenium and zinc.

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TI HIV gene expression enhances **T cell** susceptibility to hydrogen peroxide-induced apoptosis.

SO AIDS Research and Human Retroviruses, (1993) Vol. 9, No. 11, pp. 1107-1113.
ISSN: 0889-2229.

AU Sandstrom, Paul A.; Roberts, Beverly; Folks, Thomas M.; Buttke, Thomas M. (1)

AB A human **T cell** lineage was used to determine the possible effects of HIV infection on **T cell** antioxidant status. On inoculation into serum-free culture, 8E5, a constitutive HIV-expressing **T cell** line, underwent apoptosis whereas cell death was not observed with the uninfected A3.01 or latently HIV-infected 8E5L **T cell** lines. 8E5 survival was markedly prolonged by supplementing the serum-free medium with either A3.01-conditioned medium, catalase, vitamin E, or 2-mercaptoethanol, but supplementation with **ascorbic acid**, **glutathione**, or **N-acetylcysteine** had no effect. Consistent with their being in a state of oxidative **stress**, 8E5 cells displayed reduced **levels** of catalase activity, and were more susceptible to killing by exogenous hydrogen peroxide (H-2O-2) than A3.01 and 8E5L cells. These results demonstrate an inverse correlation between HIV gene expression and antioxidant status in human **T cells**. **Enhanced** cytotoxicity of HIV-infected, antioxidant-deficient CD4 **T cells** following exposure to H-2O-2 in lymphoid tissues responding to opportunistic pathogens may contribute to the depletion of CD4 **T cells** in AIDS.

ACCESSION NUMBER: 1998:1310 PROMT
TITLE: BioDynamax Supplement - Ultra Antioxidants Tablets
MANUFACTURER: BioDynamax CATEGORY: Vitamins & Tonics
SOURCE: Product Alert, (22 Dec 1997) pp. N/A.
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ABSTRACT:
BioDynamax Ultra Antioxidants have been reformulated "to provide the most comprehensive antioxidant protection in one convenient formula." This two-tablet per day Supplement contains a combination of 21 antioxidants: beta-carotene, vitamin C, vitamin E, **N-acetylcysteine**, green tea, garlic, milk thistle, hawthorn, turmeric, quercetin, red wine extract, rosemary extract, boldo, zinc, **alpha-lipoic ***acid*** **, grape seed extract, ginkgo biloba extract, bioperine, manganese, copper and selenium. Bioperine is a trademark of the Sabinsa Corp. Tablets come in 45 ct. and 90 ct. bottles tagged, "Extra strength," with suggested retail prices of $9.19 and $20.39, respectively. Boulder, CO-based BioDynamax is the manufacturer. For sample retrieval information, please call: Marketing Intelligence Service, Ltd., (716) 374-6326.

PRODUCT CODE: *PC2834700 Vitamin, Nutrient & Hematinic Preps
EVENT CODE: *EC240 Marketing procedures
CORPORATE NAME: *BioDynamax
INDUSTRY CLASS: *ADV Advertising, Marketing and Public Relations; BUSN Any type of business
GEOGRAPHIC TERM: New: *CC1USA United States
Old: *CC1USA United States
FEATURES: COMPANY; NEWSLETTER
CAS REGISTRY NO.: **50-81-7** (VITAMIN C)
117-39-5 (QUERCETIN)
616-91-1 (**N-ACETYLCYSTEINE**)
1200-22-2 (.**ALPHA.-LIPOIC ACID**)
1406-18-4 (VITAMIN E)
7439-96-5 (MANGANESE)
7440-50-8 (COPPER)
7440-66-6 (ZINC)
7782-49-2 (SELENIUM)
7235-40-7Q, 52765-84-1Q (.BETA.-CAROTENE)